Summary of Safety and Probable Benefit

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SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Osteogenic Protein 1
Device Trade Name:	OP-1 Implant
Applicant's Name and Address:	Stryker Biotech 35 South Street Hopkinton, MA 01748
Humanitarian Device Exemption (HDE) Number:	H010002
Date of Humanitarian Use Device Designation:	May 4, 2001
Date of Panel Recommendation:	The HDE was not taken to the Orthopedic and Restorative Devices Panel for review (refer to Section XII for discussion).

Date of GMP Inspection:

West Lebanon, NH: August 9, 2001

Wilder, VT: August 9, 2001

Hopkinton, MA: August 15, 2001

Date of Notice of Approval to Applicant: October 17, 2001

II. INDICATIONS FOR USE

OP-1 Implant is indicated for use as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed.

III. CONTRAINDICATIONS

- OP-1 Implant should not be used to treat patients who have a known hypersensitivity to the active substance or to collagen.
- OP-1 Implant should not be applied at the site of a resected tumor which is at or near the vicinity of the defect/fracture or in patients with a history of malignancy.
- OP-1 Implant should not be administered to patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).

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- OP-1 Implant should not be administered to pregnant women. The potential effects of OP-1 treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-1 have shown that small amounts of OP-1 will cross the placental barrier.

IV. WARNINGS AND PRECAUTIONS

See Warnings and Precautions in the final labeling (Package Insert). A patient brochure is available for use in counseling the patient.

V. DEVICE DESCRIPTION

OP-1 Implant is an osteoinductive bone graft material containing recombinant human Osteogenic Protein 1 (OP-1) and bovine bone derived collagen (ratio is 3.5mg OP-1 to 1g collagen). (OP-1 is also known as bone morphogenetic protein-7 or BMP-7.) OP-1 Implant is provided in a glass vial as a sterile, dry powder in the amount of one gram. The glass vial is sealed with a stopper and a crimp. Each vial is packaged in a thermoform tray and supplied in a box for convenient storage.

Storage: 2-8°C
Shelf-life: 18 months when stored at recommended temperature.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The following are possible alternative procedures or treatments for long bone nonunion.

- Autograft - when bone is taken from one part of the body and placed at the site of injury
- No treatment - some nonunions may be left untreated.
- Bone Growth Stimulators - devices that apply electrical energy to fracture sites to promote healing
- Amputation - the removal of a part of the body with surgery.

VII. MARKETING HISTORY

OP-1 Implant received market authorization in Australia on April 4, 2001 and in the European Union through a centralized approval application on May 17, 2001 under the regulations governing pharmaceuticals.

OP-1 Implant has not been withdrawn from marketing for reasons related to the safety and effectiveness of the product.

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VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events relevant to an orthopedic procedure occurring in >1% of 122 patients who participated in a multicenter trial of OP-1 Implant are listed in Table 1. No deaths were reported during the 24 month study period. Nearly all adverse events were classified as mild or moderate. Only three patients (2 Autograft; 1 OP-1 Implant) experienced a severe event during the 24 month study period. In the autograft group, these events were fracture of the cervical spine, and pain and decreased mobility. One patient experienced clinical depression in the OP-1 Implant group. None of these three events were recorded as being related to study treatment.

Adverse events that were clearly relevant to an orthopedic procedure for the treatment of nonunion or whose incidence was of significant interest to an orthopedic surgeon are reported in Table 1. Adverse events listed below the table typically occurred in only a few patients.

Table 1: Summary of Adverse Events for All Treated Patients in the Tibial Nonunion and Long Bone Nonunion Studies

Adverse Event Description	Tibial Nonunion Study		Long Bone Nonunion Study
	OP-1 Implant n=61	Autograft n=61	OP-1 Implant n=29
Musculoskeletal			
Hardware Complication	28/61	40/61	6/29
Nonunion	7/61	4/61	5/29
Osteomyelitis	6/61	15/61	7/29
Malunion	3/61	0/61	1/29
Injury Resulting from Fall	3/61	3/61	2/29
Hardware removal	2/61	1/61	0/29
Tendonitis (patellar, Achilles)	2/61	1/61	0/29
Contracture	1/61	3/61	1/29
Fracture (other)	1/61	3/61	0/29
Fracture (tibia, fibula)	1/61	3/61	1/29
Skin and Wound			
Wound Infection	18/61	14/61	5/29
Local Inflammation, rash, redness, itching	12/61	10/61	0/29
Swelling (ankle, foot, leg)	7/61	8/61	2/29
Blisters, skin abrasions	5/61	0/61	0/29
Neural			
Pain (ankle, knee, leg)	27/61	22/61	12/29
Neuralgia (numbness)	5/61	6/61	3/29
Pain (other)	3/61	3/61	3/29
Nerve Injury	2/61	2/61	0/29
Cardiovascular			
Hematoma	4/61	8/61	3/29
Anemia	4/61	5/61	1/29
Gastro-Intestinal			
Nausea, vomiting	18/61	19/61	3/29
Gastro-intestinal upset (indigestion, constipation, diarrhea)	7/61	5/61	1/29
Systemic and Other Complications			
Fever	31/61	29/61	0/29
Normal Surgical Complications	10/61	8/61	0/29
Drug Allergy (morphine, antibiotics)	2/61	5/61	1/29

Other events include: amputation of toe, aortocoronary bypass with valve replacement, arthritis, arthroscopy, arthrosis, athlete's foot, bruising, burning sensation, cardiac complications following surgery, chondrectomy, chondromalacia, cold symptoms/upper respiratory infection, death-unrelated causes, depression, dizziness, ear infection, fatigue, gangrene, headache/migraine, incontinence, insomnia, meniscal tear, muscle spasm, muscular herniation, myositis ossificans, nosebleeds, pancreatitis, peptic ulcer, plantar fascial fibromatosis, post operative bleeding, sciatica, skin graft, short term memory loss, shortness of breath, slow or decreased urination, stiffness, sweating, thrombophlebitis, thrombosis, urinary tract infection, weight loss, wound dehiscence, yeast infection.

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In addition, adverse event data has been collected from over 500 patients treated with OP-1. These patients were from clinical U.S. investigational device exemptions studies and international clinical studies and compassionate use information.

In total, five patients reported the occurrence of cancer. Four of the 5 events reported non-osseous cancers of varying type and location occurring in elderly patients. One patient had a mantle cell lymphoma of the colon which lead to death in a 76 year old female and an 83 year old male had a pancreatic tumor with multiple metastases which led to death. Of the other two patients, a 60 year old male had a right occipital basal cell carcinoma and the other a 79 year old male had gastric carcinoma both of whom recovered. A fifth patient was in the study with a history of recurring chondrosarcoma who had resection arthroplasty in 1985 followed by a hip revision in 1991 and fracture of the prosthesis in 1999; OP-1 was used with allograft in a total hip revision. The treating physician believes the recurrence may have presented on a thalium scan prior to treatment with OP-1. Recurrence and disease progression were considered normal for this type of cancer. An additional patient had a nonunion of a pathologically fractured femur after radiotherapy to the site of lymphoma 7 years prior to treatment with OP-1; the patient had no adverse events or recurrence. In addition, there have been four reports of heterotopic bone formation reported, with no subsequent report of a cancer related events.

Eight out of more than 500 patients treated with OP-1 experienced 10 events related to urinary or renal systems. All 10 events were considered by the treating physicians as unrelated to study treatment and were mild to moderate in severity. No severe adverse events of this nature were reported. Events included urinary tract infection (5), slow urination (1), decreased urine output (1), urinary retention (1) and retrograde ejaculation (2). Many of these events were reported immediately post-treatment and can be attributed to catheterization during and after surgery.

One patient in the long bone nonunion study had a history of renal failure secondary to an allergic reaction to penicillin 2.5 years prior to treatment with OP-1. After treatment with OP-1, the patient had no adverse events related to renal function. One patient treated under the compassionate use in Australia was on kidney dialysis at the time of treatment with OP-1; no adverse events related to renal function were reported following treatment with OP-1 in this patient. Decreased urine output was reported in one patient in the long bone study 11 months after surgery with OP-1 but resolved in 8 days.

IX. SUMMARY OF PRECLINICAL STUDIES

The safety of OP-1 Implant was evaluated in accordance with tests described in ISO 10993. Extensive biocompatibility and safety testing has been performed using OP-1 Implant, including cytotoxicity, sensitization, genotoxicity, hemocompatibility, implantation and systemic toxicity and biodistribution. Additional studies, including safety pharmacology, reproductive toxicity, pharmacokinetics, and tissue distribution studies have been performed using the OP-1 protein alone. The results of this extensive biocompatibility and safety testing, performed in a range of *in vitro* cell-

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based studies and *in vivo* animal studies (Table 2), suggest the safety of OP-1 Implant for bone repair.

Table 2: Safety Tests for OP-1 and OP-1 Implant

Test	Study	RESULTS
Sensitization	Modified Buehler Technique	Negative
	Epicutaneous Maximization Test	Negative
	Murine Collagen Type 2 Arthritis Model	Negative
Genotoxicity	Ames *Salmonella E. Coli* Reverse Mutation assay	Negative
	Chromosomal aberration test in CHO cells with OP-1 Implant	Negative
Cytotoxicity	L929 Agar Overlay Assay	Negative
	CHO Mammalian Cell Cytotoxicity Assay on OP-1 (OP-1 Implant)	Invalid: Test system incompatible with OP-1 Implant. Results inconsistent with known biocompatibility with CHO cells.
Hemocompatibility	Hemolysis Test	Negative
Implantation & Systemic Toxicity	Rat Acute Subcutaneous Implantation Study	No adverse toxic effects observed.
	Rat 22 Day Subcutaneous Implantation Study	No adverse toxic effects observed.
	Rat 13 Week Subcutaneous Implantation Study	No adverse toxic effects observed.
	Dog Tibial Implantation Study – Healing Timecourse	No adverse toxic effects observed.
	Hamster Submucosal Implantation Study	Negative.
	Healing of Tibial Segmental Defects in Dogs: Long Term Implantation	No adverse toxic effects observed. Presence of anti-OP-1 and anti-collagen antibodies did not correlate with clinical observations. No evidence of neoplastic or pre-neoplastic abnormalities long term (18 months).
	104 week Carcinogenicity Study in Rats with Subcutaneous Implantation with 52 week Toxicity Study	Tumors were found at the site of implantation in OP-1 treated animals. These results are believed to be consistent with the solid state carcinogenesis phenomenon observed when objects are implanted in rats.
	Comparative 4-week Toxicity Study in Cynomolgus Monkeys	Paravascular fibrosis and subintimal vasculopathy occurred at the injection sites in the saphenous veins; related to intravenous administration of OP-1 and not considered relevant to intraosseous implantation.
Implantation & Systemic Toxicity Continued	28 Day Repeat Dose Intravenous Study in Rats	Negative
	Acute Intravenous Study in Rats	Negative
	OP-1 Acute Intravenous Toxicity Test in Mice	Negative
Reproductive Toxicity	Development Toxicity Dose Range with OP-1	Negative
	Placental Transfer in Rat following Single Intravenous Administration	Placental transfer of ^{125}I-OP-1 to rat fetal tissue was <1%.
	OP-1 administered intravenously on embryo-fetal development in rabbits	No observable effect determined at 0.4 mg/kg/day.
	OP-1 administered intravenously on embryo-fetal development in rats	No observable effect level determined at 0.4 mg/kg/day.
Pharmacokinetics/ Biodistribution	Pharmacokinetics Following Single Intravenous Administration to Male Rats	Elimination of OP-1 from serum was rapid and biphasic. Results suggest renal clearance. Results suggest OP-1 is not distributed in to deep compartments in the tissues.
	Pharmacokinetics Following Single Intravenous Administration to Male Cynomolgus Monkeys	Elimination of OP-1 from serum was rapid and biphasic. Results suggest renal clearance. Results suggest OP-1 is not distributed into deep compartments in the tissues.
	Pharmacokinetics and Tissue Distribution of OP-1 Protein	Elimination of OP-1 from serum was rapid. Results suggest uptake of OP-1 from blood by liver. Results suggest OP-1 is not distributed into tissues. Uptake into thyroid considered associated with free ^{125}I.
	Rat Subcutaneous Implantation Study – Biodistribution of I-OP-1 Labeled Implant	No significant quantity of OP-1 is detected systemically. OP-1 eliminated from implantation site by 21 days.
	Rabbit Intraosseous Implantation Study – Biodistribution of ^{125}I-OP-1 Labeled Implant	No significant quantity of OP-1 is detected systemically.
Safety Pharmacology	Effect of OP-1 in the Irwin test in rats	Negative
	Cardiovascular effects of OP-1 in conscious telemetered rats.	Transient observations of increased blood pressure, bradycardia, tachycardia, and slight increase in body temperature to excess dose of intravenously administered OP-1 not considered cause for concern regarding intended use of intraosseous implantation.

Pharmacokinetic studies following intravenous administration of OP-1 suggest that any OP-1 which may become systemically available following intraosseous

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application of OP-1 Implant would be quickly cleared. These studies performed in rats and primates establish that OP-1 is cleared from the blood in a biphasic manner ($t_{½\ elimination} < 12$ hours). The OP-1 is not distributed into deep tissue compartments. Pharmacokinetic data suggests that OP-1 is quickly removed from the blood through the kidneys. It is excreted from the body through the urine.

In addition, several animal studies were performed which support the probable benefit of OP-1 Implant in a range of evolutionary divergent species from rats to non-human primates. The studies were performed in a wide range of orthotopic sites, including long bone, cranial and maxillo-facial applications (Tables 3 and 4).

The results obtained from these studies show that OP-1 Implant is bioresorbable, osteoinductive, and osteoconductive. The product also provides a physical scaffold in the form of collagen particles to support bone formation. The preclinical data demonstrate that new bone is formed as a direct consequence of surgical implantation of OP-1 Implant in either a bony site defect or a void. Mechanical testing data shows that the natural mechanical strength of the treated defects can be restored. Comparisons between autograft bone and OP-1 Implant show that, in some of the animal models, defects treated with the OP-1 Implant had increased mechanical strength.

Table 3: Summary of preclinical studies: Bioactivity of OP-1 Implant (Long Bone Fracture Models)[1,2,3,4]

Study	Species	Evaluations	Findings
Ulna Segmental Gap Defect	Rabbit	Radiographs Histology Mechanical (torsion) testing	OP-1, in a collagen matrix, can be implanted effectively.
Ulna Segmental Gap Defect	Dog	Radiographs Histology Mechanical (torsion) testing	A dose of 3.5 mg/gm collagen matrix is effective in healing critical size defects in a large mammal species.
Ulna Defect (Enhancement of autograft or allograft)	Dog	Radiographs Histology Mechanical (torsion) testing	OP-1, in combination with either allograft or autograft was effective in healing critical size defects.
Ulna Defect (20 weeks)	Monkey	Radiographs Histology Mechanical (torsion) testing	OP-1 was more effective in healing a nonunion gap in a non-human primate model.
Ulna Defect (time-course study)	Monkey	Radiographic analysis Computed Tomography MRI Bone mineral density measurement Mechanical testing Histology	New bone formation was seen on x-rays at three weeks. CT and MRI showed increased mineralization of the new bone by twelve weeks. A significant increase in bone mineral content was observed from three to twelve weeks. Histologic sections at twelve weeks showed calcifying tissue, chondrocytes and osteoblasts and immature woven bone. At twenty weeks, the new bone was continuing to mature.
Tibial Segmental Gap Defect	Monkey	Radiographs Histology Mechanical testing	OP-1 completely restored the bone bridging of the critical size defect. Mature bone was generated faster in the OP-1 treated defects. There was good bone formation in close opposition to the intramedullary rod.
Tibial Segmental Gap Defect (time-course study)	Dog	Radiographs, Duel Energy Xray Absorption (DEXA) scans, Nondestructive biomechanical test, Acoustic impedance imaging, Histology	All specimens showed new bone on radiographs. At 2 weeks, there was extensive formation of immature bone. By 4 weeks, mature bone was seen in the periphery, and early bridging was seen. Evidence of union was seen at six weeks. By 8 weeks the new bone had matured and remodeled. At 12 weeks, radiographic union with bridging bone throughout the defect was observed. DEXA showed all specimens had bone formation.

Table 4: Summary of Preclinical Studies: Bioactivity of OP-1 Implant (Models other than Long Bone Fracture Repair)

Study	Species	Evaluations	Findings
Cranial Defect	Baboon[5,6]	Histomorphometry	Histology showed new bone formation from the periphery to the central core after rapid angiogenesis and mesenchymal cell migration in apposition to the collagenous matrix. New bone filled with fully differentiated bone marrow elements as early as day 15, even with the 0.1 mg dose of OP-1. At one year, restoration of the internal and external cortices of the calvaria was seen. Exuberent and ectopic bone formation was observed with the highest dose displacing the temporalis muscle.
Sinus Augmentation	Chimpanzee[7,8]	Radiography (CT scan) Histology (of lateral biopsies)	Radiographic analysis: dose-dependent increased mineralization rate (also, the height from sinus floor was dose-dependent). Histomorphometric analysis showed mature, remodeled bone at 7.5 mos. Controls showed poor resorption and the matrix showed partial bony growth.
Dental-Implant Fixation	Dog[9]	Radiographs Histology	At 12 weeks: extraction sites treated with OP-1 completely filled. New bone in untreated sites showed less density, remodeling, and incorporation.

X. SUMMARY OF CLINICAL INFORMATION

Two clinical studies were performed under Investigational Device Exemptions which included patients with long bone nonunions.

U.S. Tibial Nonunion Study[10]

A prospective, randomized, controlled, multi-center study was performed to evaluate the ability of OP-1 Implant to safely heal tibial nonunions. Study entry required that each patient failed to heal following conventional treatment. Therefore, healing could be attributed solely to the investigational treatment. All patients received intramedullary nailing (IM rod) to standardize mechanical stabilization of the fracture. Patients having tibial nonunions acquired secondary to trauma and requiring autograft and IM rod fixation were enrolled. Each patient was required to have a nonunion for at least 9 months, without surgical intervention or signs of healing for at least 3 months prior to the investigational treatment. Subgroup analysis was performed for those patients who had failed prior autograft before being enrolled into the study. This analysis is presented below.

Blinding: Because of the requisite donor site surgery associated with the control group, it was not possible to blind patients and physicians to treatment type. However, blinding was used for the independent review of all study radiology. Three radiologists were blinded to treatment group, site, patient history and study time point. (Confidentiality of patient identification was maintained.)

Patient Population: Patients were randomized equally between OP-1 Implant (up to 2 units) and autograft (amount determined by surgeon). The study included 18 investigational sites, with a total of 122 skeletally mature patients with 124 tibial nonunions. There were 61 patients with 61 nonunions in the autograft treatment

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group and 61 patients with 63 nonunions in the OP-1 Implant treatment group (one patient had bilateral nonunions of the tibia; another had a proximal and distal nonunion in the same leg).

Of the 122 patients enrolled in the study, there were 26 OP-1 Implant and 19 autograft patients who had failed autograft prior to being enrolled in the study.

Baseline Demographics:
The OP-1 Implant group was 73% male (19/26), and the autograft group was 79% male (15/19). Height was comparable for both treatment groups. The nonunions included in this study began as fractures caused by high energy trauma (e.g. motor vehicle accidents), which are more likely to lead to nonunion. National Highway Traffic Safety Administration statistics report that 75% of all motor vehicle accidents occurring in the U.S. in 1998 involved male drivers. Therefore, the likelihood of men sustaining this type of injury is higher than that of women.

Table 5: Demographics and Risk Factors

Risk Factor	OP-1 Implant n=26 patients (27 nonunions)	Autograft n=19 patients (19 nonunions)
Nonunion Duration (Months) Median Mean ± Std. Dev.	 28 40 ± 34	 26 40 ± 35
Atrophic Nonunion	11/27	8/19
Comminuted Fracture at Injury	18/27	11/19
Grade III (a-c) Fracture at Injury	13/27	6/19
Open Fracture at Injury	20/27	9/19
Prior Autograft	27/27	19/19
Prior IM Rod	18/27	11/19
Tobacco/Nicotine Use (based on # of patients)	17/26	13/19
Age (Years) Median Mean ± Std. Dev.	 33 38 ± 17	 32 32 ± 7
Weight (Pounds) Median Mean ± Std. Dev.	 158 161 ± 37	 192 200 ± 46

Study Endpoints: Radiographic success was based on evidence of bridging in 3 of 4 views, as evaluated at 9 months post-treatment by consensus of two out of three independent radiologists. Clinical success was determined by the level of weight-bearing and the amount of pain experienced by the patient upon weight bearing. Full weight bearing with less than severe pain was considered a clinical success. Patients who received additional surgical interventions to promote healing at the nonunion site were considered failures for all analyses. Both the clinical and radiographic success parameters were required for classification as a comprehensive success in the study

Safety was assessed from medical events, treatment related events, laboratory tests, medication use and blood loss.

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Success Rates:
Success was analyzed utilizing the radiographic and clinical outcomes. Both the radiographic and clinical success parameters were required for classification as a comprehensive success in the study. Data from the subset of 14 patients who had a history of failed prior autograft, who met the protocol criteria, and who had data at 9 months post-treatment with OP-1 Implant, are presented in Table 6.

Table 6: Patients with Prior Failed Autograft Meeting Success Criteria at 9 Months Follow-up

	OP-1 Implant N=14	Autograft N=13
Comprehensive	7/14	11/13
Clinical	12/14	12/13
Radiographic (Bridging in 3 views)	8/14	12/13

Safety Analyses:
Safety data is presented for the subset of patients with prior autograft, however, further confirmation of safety in all patients enrolled in the study is also provided as this is relevant to the safety of OP-1 Implant in humans.

Analysis of the subset of patients with history of prior failed autograft is presented to confirm safety in the proposed indication. Following this, analysis of safety data for all treated patients (regardless of history of prior autograft) is presented in order to give a comprehensive profile of all safety data relevant to the exposure to OP-1 Implant.

Safety Data for Prior Failed Autograft Patients:
All patients reported at least one adverse event. Table 7 summarizes adverse events reported by the physician as related to treatment for each of the two groups.

Table 7: Summary of Treatment Realated Adverse Events (AEs) for Patients with Prior Failed Autograft

	OP-1 Implant N=26		Autograft N=19	
Treatment Related Events	Swelling	N=1	Donor site pain	N=4
	Persistent Nonunion	N=1	Hematoma at Donor Site	N=1
	Drainage	N=1	Ecchymosis at Donor Site	N=1
			Infection at Donor Site	N=1
Total	**3 events (2 patients)**		**7 events (5 patients)**	

Safety Data for All Treated Patients:
As previously seen in Table 1, all 122 treated patients reported at least one adverse event. Table 8 summarizes adverse events reported by the physician as related to treatment for each of the two groups.

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Table 8: Summary of Treatment Related Adverse Events (AEs) for All Treated Patients

	OP-1 Implant N=61		Autograft N=61	
Treatment Related Events	Persistent Nonunion	N=3	Donor site pain	N=5
	Erythema/swelling	N=2	Hematoma at Donor Site	N=1
	Drainage	N=1	Seroma at Donor Site	N=1
			Ecchymosis at Donor Site	N=1
			Numbness at Donor Site	N=1
			Infection w/drainage at Donor Site	N=1
			Persistent Nonunion	N=1
			Broken IM rod	N=1
			Stress Fracture at original fracture site	N=1
Total	**6 events (5 patients)**		**13 events (11 patients)**	

Very low titers of circulating antibodies to OP-1 developed in 23/61 (38%) patients treated with OP-1 and 8/61 (13%) patients treated with autograft. Three (5%) OP-1 Implant patients developed circulating antibodies to type 1 collagen. All but one of these patients had a very low titer response. Review of the individual patient records revealed no direct correlation between medical events or treatment success and the presence of anti OP-1 or anti collagen type I activity in the blood.

U.S. and Canadian Treatment Study of OP-1 Implant in Long Bone Nonunions

This prospective, non-randomized, multicenter study evaluated the ability of OP-1 Implant to safely heal long bone nonunions utilizing the patient as his own control. The inclusion criteria included only those patients with long bone nonunions who required autograft, but had failed prior autograft attempts or were not eligible for autograft. Mechanical stabilization of the fracture was allowed to vary as appropriate for the individual fracture. Each patient was required to have a nonunion for at least 9 months, without surgical intervention or radiographic/clinical evidence of healing for at least 3 months prior to the investigational treatment.

Study Design: All patients received OP-1 Implant (average of 2 units, maximum of 4 units). No control treatment was performed.

Study Centers and Randomization: Six investigational sites (5 U.S. and 1 Canadian) enrolled patients. Twenty-nine patients were treated and are eligible for analysis, 25 in the U.S. and 4 in Canada. Treated fractures included 17 of the tibia, 8 of the femur, and 4 of the humerus. Table 9 below summarizes the risk factors for healing in this patient population and the incidence of these factors for all treated patients.

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Table 9: Demographics and Risk Factors

Risk Factor and Demographics	N = 29
Nonunion Duration (months) Median Mean ± S.D.	 38 67 ± 81
Atrophic Nonunion	14/29
Comminuted Fracture at Injury	16/29
Open Fracture at Injury	11/29
Grade III, IIIa, IIIb, or IIIc Fracture at Injury	10/29
Prior Autograft	24/29
Tobacco/Nicotine Use	23/29
Age (years, mean ± S.D.)	49 ± 18
Weight (pounds, mean ± S.D.)	191 ± 53

Study Endpoints: Success was based on no further retreatment of the surgical site, clinical evaluation of function and pain at the nonunion site, and radiographic evidence of bridging in 3 out of 4 cortices as determined by consensus of two independent radiologists. Safety was assessed from adverse events and laboratory tests.

Success Rate Analysis:
Success was evaluated based on radiographic and clinical outcomes without further surgical intervention. The criteria for success were:

1. Less than severe pain;
2. In lower extremity treatments, full weight bearing; or in upper extremity treatments, normal activities or slight restriction in normal activities only; and
3. $\geq$ 75% bridging callus, or 3 out of 4 cortices bridged by radiographic assessment; and

Both the radiographic and clinical success parameters were required for classification as a comprehensive success in the study. Data from the subset of 10 patients who met the protocol criteria, and who had data at 9 months post-treatment with OP-1 Implant, are presented in Table 10.

Table 10: Patients Meeting Success Criteria at 9 Months Follow-up

	OP-1 Implant N=10
Comprehensive	1/10
Clinical	7/10
Radiographic (Bridging in 3/4 cortices)	2/10

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Safety Analysis:
Evaluation of safety parameters indicated 26 (87%) reported adverse events, with 21 patients reporting at least one serious adverse event. Two adverse events, both of mild severity, were suspected as related to OP-1 Implant: one patient reported myositis ossificans presenting as bone forming in the free flap, and one patient reported suspected immune response presenting as erythema and ecchymosis. The patient with a suspected immune response did not exhibit an increase in antibody level in the blood. Both events resolved without treatment and sequelae.

Five patients (17%) tested developed circulating antibodies to OP-1 and three patients (10%) developed antibodies to Type 1 collagen. All positive titres were considered relatively low. The observed low titres to both OP-1 and collagen were similar to the types of responses observed in the Tibial Nonunion Trial. Serum levels of anti OP-1 and anti Type I collagen did not indicate any untoward effect on healing. Evaluation of serum samples for anti OP-1 and anti collagen antibodies indicated no correlation with adverse events and no inhibition of bone formation. However, none of the 5 patients in the Long Bone Nonunion Study who were positive for anti-OP binding antibodies achieved a successful outcome.

XI. RISK/PROBABLE BENEFIT ANALYSIS

The results of the preclinical studies in animals demonstrate that OP- Implant:

- is capable of generating bone that fully bridges a critical size defect
- induces bone formation in a variety of long bones and animal species
- generates bone that is mechanically and histologically normal

Based on two clinical studies in human, OP-1 Implant has demonstrated probable benefit as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed, thus providing patients with a treatment for nonunion where the alternatives are either amputation or no treatment. This should allow the patient to regain some mobility and may decrease their pain on ambulation.

The use of autograft in treating long bone nonunions requires a donor site, often leading to pain and morbidity to the patient. Some nonunions may be left untreated, however, this can lead to pain, limited movement, deformity, and paralysis. Amputation of the affected limb is associated with physical and psychological disability to the patient. OP-1 Implant has the potential to eliminate the risks and complications associated with these treatment alternatives.

The pre-clinical and clinical data suggest that it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

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XII. PANEL RECOMMENDATION

This HDE was not reviewed by the Orthopedic and Restorative Devices Advisory Panel. However, the review of this HDE was done as collaboration between scientists in the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER). In addition, a review was done as a homework assignment by an outside pathology expert.

XIII. CDRH DECISION

CDRH has determined that, based on the data submitted in this HDE application, the OP-1 Implant will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on October 17, 2001. All facilities involved in the manufacture of this device have been inspected and found to be in compliance with the Quality System Regulation.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the physician's labeling.

Hazards to Health from Use of the Device: See Indications, Contraindication, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

XV. REFERENCES

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